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Vitamin D. 100 years of discoveries yet controversy continues

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History of discovery of vitamin D and recent discoveries in vitamin D metabolism (Panel)

Rickets been recognized for hundreds of years. In 1889 a disease map in England showed that rickets occurred in the industrial towns,[1] was more noticeable in spring and disappeared in the summer[2]. In 1919 sunlight and ultraviolet light (UV) were shown to cure rickets[3]. In the same year, the British biochemist and nutritionist Edward Mellanby tested multiple diets, including Scottish porridge, to induce rickets in dogs. He then cured it with cod liver oil and concluded that cod liver oil contained a fat soluble factor; either vitamin A or something similar.[4] A clinical trial published in 1922 in The Lancet showed that childhood rickets could be healed by cod liver oil, ultraviolet light and sunlight exposure and this was attributed to vitamin A.[5] In order to see if vitamin A was the active agent McCollum and colleagues in the USA oxidized cod liver oil to destroy vitamin A but found that the oil still cured rickets in rats. They hypothesized the presence of a fourth vitamin which they called vitamin D (the next letter in the alphabet). [6] Around the same time, Steenbock and Black conducted a series of experiments in which they irradiated both rats and their food with UV light and found that both procedures prevented rickets, concluding that a lipid in the diet and skin was converted by UV light into an anti -rachitic substance.[7] This process was patented and became the foundation for commercial vitamin D_2 supplementation of foods that prevented rickets thereafter. This was a momentous discovery and led to widespread vitamin D supplementation 200-400 IU daily in children in Europe and North America and the elimination of rickets.

In 1925 Hess and colleagues in New York showed that UV light could convert cholesterol to produce ergosterol. [8] They used this process to treat rickets and showed that one ounce of activated ergosterol was equivalent to 6 tons of cod liver oil, but it was so potent in children that it caused severe hypercalcemia.[9] Commercially irradiation of plant ergosterol produced ergocalciferol now named vitamin D2[10,11] which has been available since 1931 as 'Vigantol' and 'Haliverol'. However, the natural form of vitamin D3 was discovered in 1936 after irradiation of 7 dehydrocholesterol produced vitamin D_3[12] **().** Both vitamin D2 and D3 have been available from the 1930's to treat rickets, osteomalacia, hypoparathyroidism, and renal bone disease. Later experiments showed vitamin D2 and D3 were not biologically active but had to be converted to more active metabolites. The first metabolite discovered in 1968 was 25 hydroxyvitamin D (25OHD) [13] but the slow increase in calcium absorption suggested that there must be another active metabolite. In 1971, the active metabolite, produced in the kidney was identified as 1,25 dihydroxyvitamin D3 ($1,25(OH)_2D$).[14-16] In 1974, synthetic 1,25 dihydroxyvitamin D3 (calcitriol) became available for clinical use in renal bone disease, hypoparathyroidism and osteoporosis[17]. (**Panel**)

Vitamin D metabolism. It is now understood that 1,25 dihydroxyvitamin D3 is also a hormone and levels are homeostatically regulated by both parathyroid hormone (PTH)[18,19] via changes in serum calcium and fibroblast growth factor 23 (FGF23) via changes in serum phosphate.[20] Both PTH and FGF 23 are involved in feedback regulation of 1,25 dihydroxyvitamin D secretion, PTH stimulating formation of the hormone and FGF 23 suppressing it while 1,25 dihydroxyvitamin D3 suppresses PTH and stimulates FGF23. Initially 1,25 dihydroxyvitamin D was thought to regulate only mineral homeostasis but in the 1970's 1,25 dihydroxyvitamin D was found to bind to a receptor (VDR) present in many tissues and stimulate transcription of several hundred genes [21,22]These cells have the same enzymatic system as the kidney and can convert 25OHD to active 1,25 dihydroxyvitamin D and non-active 24,24(OH)2D.

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Measurement of vitamin D metabolites. Vitamin D3 entering the blood via skin synthesis or from diet has a half-life of 12 hours [23]; 25OHD$_3$ has a half-life of about 2 weeks [24]and serum 1,25 dihydroxyvitamin D$_3$ has a half-life of 4-6 hours.[25] Because serum 1,25 dihydroxyvitamin D3 is a hormone whose levels remain constant it is not a useful measurement for assessing vitamin D status in normal people although the level is usually low in chronic renal failure when the kidney fails to synthesize it. Measuring serum 25OHD is ideal because of its longer half-life and it is a biomarker of vitamin D exposure from sunlight and diet. Using assays for serum 25OHD, studies from 1975 in northern Europe showed evidence of extensive severe vitamin D deficiency,40 percent of people in UK had levels less than 25nmol/L (10ng/ml),[26,27] in Ireland and France 50 percent of nursing homes residents had levels less than10nmol/L(4 ng/ml), [28,29] and in Holland 79 % of nursing home patients had levels less than 25nmol/L (12ng/ml)that increased to normal with vitamin D treatment.[30] Possible reasons for such low levels in Northern Europe are the lack of adequate sunlight, especially in the winter months, and absence of dietary supplementation. Today the recommended lower normal range for serum 25OHD is 50nmol/L (20 ng/ml). To circumvent technical issues with measurement of serum 25OHD, which varies by 20-30 percent across multiple assay systems, the recent introduction of calibration standards now used by many companies, allows comparisons amongst studies. [31]

Controversies surrounding determination of the vitamin D recommended dietary allowance

The IOM (Institute of Medicine-now National Academy of Medicine) convened a committee to study available data on Vitamin D and chronic diseases. Their conclusions were that studies of vitamin D, calcium or the combination on health outcomes were inconsistent and it was not possible to synthesize a dose-response related to health outcomes.[32] In order to estimate the RDA for vitamin D, a marker or indicator was needed. Because evidence was lacking for a clinical effect of vitamin D on any system other than that of musculoskeletal health this became the indicator for determining RDA. There were several lines of evidence showing that a serum 25OHD level of greater than 50nmol/L (20ngml) was associated with lower incidence of fractures in several studies,[33,] with lower serum PTH and normalization of bone turnover markers.[33] A meta-analysis of osteoporosis trials showed that vitamin D 800 IU plus 1200mg calcium significantly reduced fractures by 8%,[34] although this result was heavily dependent on the inclusion of a large study of French nursing home women, mean age 86 years.[35] If a serum 25OHD of 50nmol/l (20ng/ml) was the target then the question was what dose of vitamin D would exceed this level. A meta regression analysis of all serum 25OHD data collected in wintertime studies in Northern latitudes when UV would have a minimal effect on vitamin D synthesis in skin showed that vitamin D 600 IU would meet a serum 25OHD of 50nmol/L in 97.5 % of the population, so the RDA was set at 600 IU for most adults. Because of lack of knowledge about vitamin D metabolism in older people, the presence of comorbidities, uncertainty about their diet, sun exposure, the RDA for elderly was increased to 800 IU[32.]

The proposed RDA immediately aroused controversy and many in the clinical bone and mineral field disagreed and thought the RDA was too low. Later that year, the Endocrine Society published clinical practice guidelines that contrasted sharply with the IOM; they recommended that a normal serum 25OHD level was 75nmol/L (30ng/ml), values between 50-75nmol/L (20-30ng/ml) indicated vitamin D 'insufficiency' and levels less than 50nmol/L (20ng/ml) represented vitamin D deficiency.[36] To meet the Endocrine Society target of 75nmol/L (30ng/ml) people were advised to take vitamin D 1,500-2,000 IU daily and up to 10,000 IU/d to correct vitamin D deficiency. As a further recommendation, the Endocrine society strongly suggested that increasing vitamin D levels higher than the American IOM recommendation might also reduce the incidence of numerous extra skeletal diseases including cancer, heart disease, falls, and depression.

These guidelines blurred the distinction between population guidelines, 600-800 IU daily outlined by the IOM, and prevention of extra skeletal disease that may need higher doses of vitamin D, but for which there

were no clinical trial data. As such, it was an experimental recommendation. Although the Endocrine Society did not directly recommend population testing in their guidelines, publicity in social media caused increased demand for vitamin D tests. Recommended levels of serum 25OHD escalated, as more association papers suggested that optimal 25OHD levels of 100-200nmol/L (40- 80 ng/ml) could reduce cancer, immune disorders and cardiovascular disease and hence would require a total daily vitamin D input from 3,000 to 9,6,00 IU.[37,38] Despite the widespread criticism of the IOM recommendation of 600 IU and a target serum 25OHD of 50nmol/L, similar recommendations using the same indicator of musculoskeletal health were formulated by many other national committees; e.g. 400 IU in the UK [39] ,600 IU by the European Food and Safety Association[40]**;** 800 IU by German Austrian, Swiss societies; [41] 400 IU to 70 years and 800 IU after 70 years of age by Nordic and Netherlands societies; [42,43]600 IU up to age 70 years and 800 IU after age 70 by Australian and New Zealand Societies.[44]

Following these two reports [32,36] interest in vitamin D increased exponentially. Because of rapid development of immunoassays for measuring 25OHD there are data from every continent in the world. Serum 25OHD levels in all continents show 30-80 percent of the general population have values less than 50nmol/L (20ng/ml) [45-48] except in summer when serum 25OHD-often increases above 50nmol/l (20ng/ml) [32] Unexpectedly, countries with high sun exposure such as Morocco, Ethiopia, Saudi Arabia, parts of Spain and Italy have as many as 70% of the population with serum 25OHD less than 50nmol/L (20ng/ml).[48] and may have 30-50 percent of people with severe vitamin D deficiency,< 25nmol/L (10ng/ml).[49] Immigrants into Western countries are commonly found to have very low serum 25OHD levels; this may be due to cultural habits which includes protective clothing and veils, both of which limit sun exposure.[45,50-51] They may also have calcium deficiency rickets. In infants and children in Africa where serum 25OHD levels are normal very low calcium intake (less than 200mg/d) is a cause of rickets and calcium 300-500mg/day alone can cure rickets.[45,47] It should be noted these studies are not population sampling, but convenience sampling based on clinics or volunteers and marked deficiency may occur in subgroups not tested. In contrast Scandinavian countries with long standing policies of vitamin D supplementation have less than 1% of their population with serum 25OHD less than 25nmol/L (10ng/ml)[46]

The next phase of vitamin D research: The discovery in 1988 **t**hat vitamin D receptors and the vitamin D enzyme system exist in most cells in the body inducing transcription of several hundred genes, led to the idea that larger amounts of vitamin D might be beneficial in preventing the onset of non-skeletal diseases such as cancer, heart attacks, depression, chest infection, diabetes[52] and other diseases.[36,53] As a result, a next phase of clinical vitamin D activity began. Very large trials were initiated in several sites around the world starting around 2005, and since then approximately 100,000 subjects have been entered into controlled randomized trials of placebo/vitamin D. To accommodate large numbers and increase compliance a pragmatic plan often used was to give very large doses (bolus) annually, quarterly, monthly, or weekly. However, in retrospect it would have been wiser to perform feasibility studies on daily versus infrequent bolus doses in view of some unusual results from these trials.

Recent results of randomized placebo-controlled trials with vitamin D.

Studies of ~ 80,000 participants in randomized vitamin D/placebo-controlled trials did not show a significant reduction in the incidence of fractures, cancer, heart disease, type 2 diabetes, upper respiratory infections, asthma (**Table**) and tuberculosis**.** In the table we review the latest trials. Although studies had a defined dose, subjects in both vitamin D and the placebo arms were allowed to continue their own vitamin D supplements and serum 25OHD reflected total vitamin D input.

Effect of vitamin D on fracture. (Table). In 10 large prospective placebo-controlled studies of ~57,000 participants, vitamin D was given bolus doses in 5 studies [54-58] and daily in 5 studies [59-63]. Subjects were followed up to 5 years. In 2 bolus studies of large single doses (300,000 IU i.m. and oral 500,000 IU) there

were significant increases in hip fractures of 82 percent in women but not men [54.] and 26 percent increase in all fractures in women that was attributed to an increase in falls.[55] In 5 studies using oral daily doses 400-2,000 IU there was no effect on fracture incidence.[59-63] Serum 25OHD on vitamin D treatment averaged 77nmol/L (range 55-132 nmol/L (24-50ng/ml) depending on dose compared to placebo 52nmol/l (21ng/ml) Subgroup analysis in 2 studies totally 28,546 subjects [61,63] were not able to show any difference in fracture on vitamin D regarding age, sex, race, BMI, osteoporosis medication, previous fracture history, baseline use of vitamin D, supplemental calcium, baseline serum 25OHD. In the largest study a subgroup of 401 subjects with serum 25OHD < 25nmol/l (10ng/ml) had a lower fracture rate as those with higher levels [63.]

Vitamin D and Falls. (Table) There have been five large well conducted placebo-controlled trials on ~55,000 subjects lasting between 2-5 years that measured the incidence of falls. [55,64-66] Bolus vitamin D doses varied from a single oral dose 500,000 IU annually[55], 100,000 IU monthly [57] or 60,000 monthly [64,] and daily doses of 2,000 IU[65] and 1,000 IU[66]. There was no significant difference in the incidence of falls between vitamin D and placebo groups. Serum 25OHD on vitamin D averaged 98nmol/L. (39 ng/ml) compared to placebo 67nmol L (27ng/ml).

Vitamin D and cancer. (Table). Studies of the effect of vitamin D on cancer incidence were collected on ~36,126 men and women in 5 placebo-controlled studies**.** Vitamin D doses ranged from bolus 100,000 IU 4 monthly or monthly and 1600 to 2,000 IU daily for up to 5 years. **T**here was no effect of vitamin D in preventing cancer.[56,67-70] On vitamin D, serum 25OHD levels ranged from median 109 nmol/L (44ng/ml) compared to 67 nmol/ (27ng/ml) on placebo. A recent meta-analysis of 10 studies including the 5 above showed no effect of vitamin D on cancer incidence but did find evidence that vitamin D reduced cancer mortality[71]; the mechanism for this effect is unknown and may be related to an effect of vitamin D on the immune system.

Vitamin D and Cardiovascular (CVD) events. (Table). In 4 large placebo-controlled studies of 31,052 participants there was no effect of vitamin D, given daily or bolus, in preventing cardiovascular events.[56,67,70,72] Serum 25OHD levels on vitamin D averaged 99 nmol/L (40ng/ml) compared to 66 nmol/L(26ng/ml) on placebo

Vitamin D and prevention of Type 2 Diabetes. (Table) Two long term randomized trials in 2,934 patients were performed to see vitamin D could delay the onset of type 2 diabetes. One study tested 20,00IU weekly for 5 years[73] and the other gave 4,000 IU daily for average of 2.5 years[74] Neither study showed any effect on preventing diabetes. Serum 25OHD levels averaged 128 nmol/L (51ng/ml) on vitamin D and 66 nmol/l (26 ng/ml) on placebo In a post hoc analysis of the 103 participants with marked vitamin D deficiency serum 25OHD < 30nmol/l (12ng/ml) there was a significant reduction in cases of type 2 diabetes (HR 0.38,95% CI 0.18-0.80).

Effect of vitamin D on Asthma. (Table) There are about 5 million children and 20 million adults with asthma in the USA and African American children who often have low serum 25OHD are particularly susceptible.[75] In a study from North America, 200 high risk children with asthma, average age 9 years who were on low dose inhaled corticosteroids were randomized to vitamin D 4,000 IU daily or placebo. There was no difference between groups in the outcome which was 'time to a severe exacerbation of asthma', it was 240 days in the vitamin D group and 253 days in placebo group.[76] In another trial of 400 adults, average age 40 years, with asthma and on low dose inhaled corticosteroids, patients were randomized to vitamin D, an initial dose of 100,000IU then 4,000 IU daily or placebo and followed for 28 weeks. The incidence rate of exacerbations of asthma was not significantly different, 28% on vitamin D compared to 29% on placebo.[77] In a meta-analysis of individual patient data on 955 patients on the effect of vitamin D on exacerbations of asthmatics needing systemic steroids, there was an overall reduction in

events RR 0.74 (0.56-0.97). A subgroup analysis of those with serum 25OHD < 25nmol/l showed a larger effect with RR of 0.33 (0.11-0.98), p=0.046.[78] A post hoc analysis of the New Zealand cardiovascular study of 5110 participants was performed in those that had a history of asthma or COPD; there were 402 cases in the vitamin D and 373 in the placebo groups. There was no significant difference in exacerbations between the two groups, however in the 60 subjects with serum 25OHD levels < 25nmol/l (10ng/ml), exacerbations occurred in 2/27 on vitamin D compared to 23/33 on placebo. (ρ< 0.005)[79]

Effect of vitamin D on the incidence of respiratory infections. **(Table)**. There have been two large bolus trials. In a study from New Zealand 5,110 adults were randomized to vitamin D, 200,000 IU initially then 100,000 IU monthly or placebo and followed for 3.5 years. The incidence of acute upper and lower respiratory infections on vitamin D supplementation was similar to placebo.[80] In a study from Australia 21,315 participants were randomized to vitamin D 60,000 IU monthly or placebo for 5 years and acute upper respiratory infections occurred similarly in both groups.[81`] A recent meta-analysis of aggregate data from 43 trials and 48,488 patients showed infections on vitamin D occurred in 61.3 percent compared to 62.3 percent on placebo with an OR 0.92 (0.86-0.99). Subgroup analysis showed that benefits were confined to small daily doses 400-1,000 IU and trials lasting less than 12 months (OR 0.78 (0.65-0.94). There was no effect of vitamin D using bolus doses, larger doses and no evidence of a threshold response related to serum 25OHD level.[82]

Tuberculosis. The effect of vitamin D in preventing Tuberculosis was performed in a study of 8,551 children in Mongolia, comparing vitamin D3 14,000 IU weekly or placebo for 3 years.[83] The primary outcome was a positive test for tuberculosis after 3 years. At the end of study there was no difference between the groups in positive TB tests, 3.6% in the D group and 3.3% in the placebo group. Serum 25OHD at baseline was very low < 30nmol/L (12ng/ml) and the level on vitamin D was 80nmol/L (32ng/ml). In a study of 4,000 patients living with HIV on ART treatment in Tanzania who are at increased risk for pulmonary tuberculosis were treated with vitamin D or placebo. Vitamin D 50,000IU weekly for 4 weeks then 2,000IU daily for one year. At the end of study, the mortality rate was similar 10 percent in each group, there was no difference in the incidence of tuberculosis HR 0.78(0.54-1.13) and no difference in hospitalizations HR 1.06(0.80-1.41).[84] These were key studies that addressed the issue of impaired immunity as a contributing cause of tuberculosis, but results do not support that theory.

Effect of vitamin D on Covid-19. Recently 2 prospective vitamin D placebo controlled trials were completed and the results in both studies were negative for prevention of Covid-19 and upper respiratory infections.[85,86] In a study in the UK 3,100 participants were randomized to daily 3200 IU or 800 IU if serum 25OHD < 75nmol/L(30ng/ml) and compared to 3100 controls; the endpoint was a positive covid PCR test and upper respiratory infections after 6 months. There was no difference between treated and untreated.[86] Study results may have been influenced by the start of the national covid vaccination program because by the end of study 89% had been vaccinated and a high number took their own vitamin supplements during study perhaps knowing they had low baseline 25OHD levels < 75nmol/L(30ng/ml)[85]. In the other study in Norway 34,741 subjects were randomized to cod liver oil containing 400 IU vitamin D or none for 6 months. Baseline 25OHD was 70.5nmol/L (28ng/ml) and by end study 67.9nmol/l (27 ng/ml). There was no reduction in positive PCR SARS test or in serious covid infection between groups.[86.]

Effect of Vitamin D on Auto immune diseases. (Table). In the 5 year VITAL trial 25,871 participants the study design was a two by two factorial design testing vitamin D 2000 IU daily and Omega 3 fatty acids 1g daily or placebo.[87] In the vitamin D only arm there was a lower incidence of overall auto immune diseases on vitamin D (n123)compared to placebo (n155), marginally significant; HR 0.78 (0.61-0.99, ρ= 0.05) If only the last 3 years of the trial were considered then the incidence of auto immune diseases was

reduced further HR 0.61;0.43-0.86, p =0.005; this result may support the latency of the treatment effect although other statistical models did not confirm a time effect and this was an unplanned analysis.

Effect of calcium combined with vitamin D on fractures. A recent meta-analysis analyzed fracture data from 7 studies conducted in community dwelling and excluded nursing home studies.[88] Treatment with calcium and vitamin D did not significantly decrease any type of fracture compared to placebo or no treatment and subgroup analysis based on calcium/vitamin D dose, baseline calcium intake, serum 25OHD and previous fracture history did not change results. Of note, the new meta-analysis showed no effect of calcium on fractures. This can in part be explained by reanalysis of the original WHI study that initially reported a reduction in hip fractures of 12 percent on calcium (HR 0.88 (0.72-1.08) [89] but the group included 18,176 women on calcium plus hormone treatment and 18,106 on placebo. In a recent latest reanalysis of the WHI study after excluding women on hormones there were 4015 on calcium/vitamin D only (total calcium intake 2100mg daily) and 3957 on placebo, a comparison between these groups showed no effect of calcium on hip fracture incidence [RR 1.20 (0.85-1.69)].[90] Thus, present evidence does not support the use of calcium and vitamin D in community living people but whether this applies to people in nursing home or those with very low calcium intake is not known.

Safety of vitamin D.

Recommendations from agencies evaluating safety of a nutrient set a Tolerable upper limit (TUL) of 4,000 IU daily[32]. It is not a recommended daily intake but estimated to be the highest daily intake above which there may be an increased risk of adverse events over the long term for most of the general population. It serves as a reference guide for policy makers, stakeholders, and researchers. Previously this recommendation was based on observational case reports of vitamin D intoxication including hypercalcemia, hypercalciuria, nephrocalcinosis, renal stones, and calcification of arteries.[32] It is impossible ethically to conduct a deliberate study of vitamin D intoxication thus we have to rely on case reports from literature and studies performed in animal models; toxicity studies from rats[91] show similar findings to those humans including hypercalcemia and hypercalciuria and it has been suggested that 25OHD rather than calcitriol is the cause and findings from case reports suggest doses of 10,000-40,000 IU daily can produce toxicity.[32]

Because of uncertainty about the small numbers of case reports the TUL of 10,000 IU daily was reduced to 4,000 IU daily for all adults.[32] However, the TUL applies to vitamin D only and there is no guidance for when vitamin D combined with calcium but when smaller doses of vitamin D 800-2000 IU are combined with calcium as in the milk alkali or calcium alkali syndromes it can more easily cause vitamin D intoxication and long term renal damage especially in the elderly.[92,93] A study of vitamin D doses 400 - 4800 IU combined with a calcium intake of 1200mg /d as recommended by National Osteoporosis Societies produced hypercalciuria in 30 percent of older women.[94] The limitations of deriving a TUL are the lack of knowledge about long term adverse effects of high daily doses not associated with classic vitamin D intoxication, although evidence is emerging that even lower daily doses less than 4,000 IU may have adverse effects.

The paradigm is shifting. Classic vitamin D intoxication is characterized by hypercalcemia, hypercalciuria and nephrocalcinosis.[32,91] Recent vitamin D trials, however, report new and unexpected adverse events without signs of vitamin D intoxication; these include increased fractures after annual injections of 300,000 IU [55] and after annual bolus oral doses of 500,000 IU[54] .Increased falls after 500,000 annually[54]; increased injurious falls, hospitalizations and death on daily doses of 1,000 IU 2,000 IU and 4,000 IU/daily.[66] An increase in peripheral bone loss after 3 years on daily doses of 4,000 and 10,000IU daily compared to 400 IU daily.[96] There are few longitudinal studies of the effect of vitamin D where the primary outcome was time to first fall or death. In the STURDY trial the group on 1,000 IU compared to

200 IU had more serious falls HR 1.87(1.03-3.4), and falls leading to hospitalization HR 2.48 (1.13-5.46). For these same outcomes rates were higher on 4,000IU HR1.68(0.86-3.27).[66] Notably these events occurred in elderly women average age 77 years.

Summary. For the general population, evidence suggests the generally accepted RDA for vitamin D 600-800 IU/d should be continued, since larger doses that increase serum 25OHD > 75nmol/L (30ng/ml) have failed to reduce disease burden and, in fact, appear to have caused harm in the older population. Using this guideline there should be no need to measure serum 25OHD in the normal population but in people at higher risk with diseases that may affect vitamin D metabolism, for example in patients with malabsorption syndromes, steroid therapy or older people who are housebound when measurement of serum 25OHD can be clinically helpful.

Where do we go from here? These trials were performed in the healthiest and wealthiest groups in the population. Future research studies need to be performed in underserved populations who often have very low levels of vitamin D 25nmol/L (<10ng/ml), poorer nutrition and a higher burden of chronic diseases. From the subgroups analysis of patients with serum 25OHD levels < 25nmo/l (10ng/ml) results suggest a relationship with type 2 diabetes, upper respiratory infections, and asthma but confirmatory trials in these groups are needed. Future vitamin studies should recruit participants from this group. This will only be possible with multicenter studies or consortia using a common protocol.

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References

1. Owen I. Geographical distribution of rickets, acute and sub-acute rheumatism, chorea, cancer, and urinary calculus in the British islands. Brit. Med. J.1889 I: 113–116
2. Schmorl CG. Die Pathologische anatomie der rachitischen knochenerkrabkuwa. Ergebn.Inn. Med Kinderheilk4:403,1909
3. Huldschinsky, K. Heilung von Rachitis durch Kunstliche Hohensonne. Deutsch. Med. Woch.1919 45: 712–713
4. Mellanby E. An experimental investigation on rickets. Lancet 1919; 1:407–412. [a new vitamin he called D
5. Chick, H., Dalyell, E. J., Hume, M, et.al. The aetiology of rickets in infants: prophylactic and curative observations at the Vienna University Kinderklinik. Lancet, 1922 ii: 7–11
6. McCollum EV, Simmonds N, Becker JE, Shipley PG. An experimental demonstration of the existence of a vitamin which promotes calcium deposition. J Biol Chem 1922; 53:293–298
7. Steenbock H, Black A. Fat-soluble vitamins. XXIII. The induction of growth-promoting and calcifying properties in fats and their unsaponifiable constituents by exposure to light. J Biol Chem 1925; 64:263–298.
8. Hess, A. F., Weinstock, M. & Heelman, F. D. (1925) The antirachitic value of irradiated phytosterol and cholesterol. J. Biol. Chem. 63: 305–309.
9. Hess A, Lewis J M. Clinical experience with irradiated ergosterol. JAMA 1928,91(11)783-788.
10. Windhaus A. (1931) The chemistry of irradiated ergosterol. Proc. R. Soc. (Lond.) 108: 568 –575.

11. Askew FA, Bourdillon RB, Bruce HM, et.al. The distillation of vitamin D2. Proc R Soc 1931; B107:76
12. Windaus, A., Schenck, F. & Werder, F. V. 1936. Uber das anti rachitisch wirksame Bestrahlungsprodukt aus 7-Dehydrocholesterol. Z. Physiol. Chem. 241: 100–103.
13. Blunt JW, DeLuca HF, Schnoes HK. 25-Hydroxycholecalciferol. A biologically active metabolite of vitamin D3. Biochemistry 1968; 7:3317–3322
14. Holick MF, Schnoes HK, DeLuca HF. Identification of 1,25-dihydroxycholecalciferol, a form of vitamin D3 metabolically active in the intestine. Proc Natl Acad Sci USA 1971;68: 803–804.
15. Lawson DEM, Fraser DR, Kodicek E, Morris HF, Williams DH. Identification of 1,25dihydroxycholecalciferol, a new kidney hormone controlling calcium metabolism. Nature 1971; 230:228–230.
16. Fraser DR, Kodicek E. Unique biosynthesis by kidney of a biologically active vitamin D metabolite. Nature 1970; 228:764–766.
17. Gallagher JC, Riggs BL, Eisman J, Hamstra A, Arnaud SB, DeLuca HF. Intestinal calcium absorption and serum vitamin D metabolites in normal subjects and osteoporotic patients: effect of age and dietary calcium. J Clin Invest. 1979 Sep;64(3):729-36
18. Boyle IT, Gray RW, DeLuca HF. Regulation by calcium of in vivo synthesis of 1,25dihydroxycholecalciferol and 21,25-dihydroxycholecalciferol. Proc Natl Acad Sci USA 1971; 68:2131–2134.
19. Garabedian M, Holick MF, DeLuca HF, Boyle IT. Control of 25-hydroxycholecalciferol metabolism by parathyroid glands. Proc Natl Acad Sci USA 1972; 69:1673–1676
20. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. J Bone Miner Res. 2004 Mar;19(3):429-35.
21. Haussler MR, Myrtle JF, Norman AW. The association of a metabolite of vitamin D3 with intestinal mucosa chromatin in vivo. J Biol Chem. 1968; 243:4055–64.
22. Baker AR, McDonnell DP, Hughes MR, et al. Cloning and expression of full-length cDNA encoding human vitamin D receptor. Proc Natl Acad Sci USA. 1988; 85:3294–8.
23. Mawer EB, Lumb GA, Stanbury SW. Long biological half-life of vitamin D3 and its polar metabolites in human serum. Nature. 1969 May 3;222(5192):482-3.
24. Jones KS, Assar S, Harnpanich D, Bouillon R, Lambrechts D, Prentice A, Schoenmakers I. 25(OH)D2 half-life is shorter than 25(OH)D3 half-life and is influenced by DBP concentration and genotype. J Clin Endocrinol Metab. 2014 Sep;99(9):3373-81
25. Clements MR, Davies M, Hayes ME, Hickey CD, Lumb GA, Mawer EB, Adams PH. The role of 1,25-dihydroxyvitamin D in the mechanism of acquired vitamin D deficiency. Clin Endocrinol (Oxf). 1992 Jul;37(1):17.
26. Corless D, Beer M, Boucher BJ, et.al. Vitamin D status in long-stay geriatric patients. Lancet 1975.1:1404.
27. Baker MR, McDonnell H, Peacock M, Nordin BE. Plasma 25-hydroxy vitamin D concentrations in patients with fractures of the femoral neck. Br Med J. 1979 Mar 3;1(6163):589
28. McKenna MJ, Freany R, Meade A, Muldowney FP 1985 Hypovitaminosis D and elevated serum alkaline phosphatase in elderly Irish people. Am J Clin Nutr 41:101
29. Chapuy MC, Durr F, Chapuy P. Age-related changes in parathyroid hormone and 25-hydroxycholecalciferol levels. J Gerontol. 1983 38:1 19-22 ,1983,
30. Lips P, Wiersinga A, van Ginkel FC, Jongen MJ, Netelenbos JC, Hackeng WH, Delmas PD, van der Vijgh WJ. The effect of vitamin D supplementation on vitamin D status and parathyroid function in elderly subjects. J Clin Endocrinol Metab. 1988 Oct;67(4):644-50.
31. Wise SA, Phinney KW, Tai SS, Camara JE, Myers GL, et.al Baseline Assessment of 25-Hydroxyvitamin D Assay Performance: A Vitamin D Standardization Program (VDSP) Interlaboratory Comparison Study. J AOAC Int. 2017 Sep 1;100(5):1244-1252.

32. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academies Press, 2011.
33. Gallagher JC, Sai AJ. Vitamin D insufficiency, deficiency, and bone health. J Clin Endocrinol Metab. 2010 Jun;95(6):2630-3.
34. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007 Aug 25;370(9588):657-66.
35. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, Delmas PD, Meunier PJ. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med. 1992 Dec 3;327(23):1637-42
36. Holick MF, Binkley NC, Bischoff-Ferrari HA, et.al. Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011 Jul;96(7):1911-30
37. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25 hydroxyvitamin D in the range associated with cancer prevention. Anticancer research.2011; 31(2):607–11.
38. Heaney RP, Armas LA, French C. All-source basal vitamin D inputs are greater than previously thought and cutaneous inputs are smaller. J Nutr. 2013 May;143(5):571-5
39. Scientific Advisory Committee on Nutrition (SACN). Vitamin D and health. Public Health England https://www.gov.uk/government/groups/scientific-advisory-committee-on-nutrition. 2016
40. EFSA Technical report. Outcome of a public consultation on the Draft Scientific Opinion of the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) on Dietary Reference Values for vitamin D. 2016 October Wiley10.1002/(ISSN)1831-4732.
41. German nutrition Society. New reference values for vitamin. Ann Nutr. Metab. June 2012.
42. Nordic Council of Ministers, 2014. Nordic Nutrition Recommendations 2012. Integrating nutrition and physical activity. Nordic Council of Ministers, Copenhagen, Denmark, 627 .2012.
43. Health Council of the Netherlands. Evaluation of dietary reference values for vitamin D. No 2012/15E, 138 .2012.
44. Nowson CA, McGrath JJ, Ebeling PR, et.al. Working Group of Australian and New Zealand Bone and Mineral Society, Endocrine Society of Australia, and Osteoporosis Australia. Vitamin D and health in adults in Australia and New Zealand: a position statement. Med J Aust. 2012 Jun 18;196(11):686-7.
45. Thacher TD, Fischer PR, Strand MA, Pettifor JM. Nutritional rickets around the world causes and future directions. Ann Trop Pediatric. 2006 Mar;26(1):1-16.
46. Hilger J, Friedel A, Herr R, et.al. A systematic review of vitamin D status in populations worldwide. Br J Nutr. 2014 Jan 14;111(1):23-45.
47. Munns CF, Shaw N, Kiely M, et.al. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets. J Clin Endocrinol Metab. 2016 Feb;101(2):394-415.
48. van Schoor NM, Lips P**.** Global overview of vitamin D status in Vitamin D: Editors Gallagher JC, Bikle DD. Endocrinol Metab Clin North Am. 2017 Dec;46(4):845-871.
49. Holvik K, Meyer HE, Haug E & Brunvand L. Prevalence, and predictors of vitamin D deficiency in five immigrant groups living in Oslo, Norway: the Oslo Immigrant Health Study. *European Journal of Clinical Nutrition* 2005 **59** 57–63.
50. van der Meer IM, Karamali NS, Boeke AJ, Lips P, Middelkoop BJ, Verhoeven I & Wuister JD. High prevalence of vitamin D deficiency in pregnant non-western women in the Hague, Netherlands. *American Journal of Clinical Nutrition* 2006 **84** 350–353.
51. Andersen R, Molgaard C, Skovgaard LT.et.al. Pakistani immigrant children and adults in Denmark have severely low vitamin D status. European Journal of Clinical Nutrition 2008 62 625–634.
52. Rosen CJ, Adams JS, Bikle DD, Black DM, Demay MB, Manson JE, Murad MH, Kovacs CS. The non-skeletal effects of vitamin D: an Endocrine Society scientific statement. Endocr Rev. 2012 Jun;33(3):456-92.

53. Garland CF, French CB, Baggerly LL, Heaney RP. Vitamin D supplement doses and serum 25 hydroxyvitamin D in the range associated with cancer prevention. Anticancer research. 2011; 31(2):607–11.
54. Smith H, Anderson F, Raphael H, et.al. Effect of annual intramuscular vitamin D on fracture risk in elderly men and women--a population-based, randomized, double-blind, placebo-controlled trial. Rheumatology (Oxford). 2007 Dec;46(12):1852-7.
55. Sanders KM, Stuart AL, Williamson EJ, et.al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA. 2010 May 12;303(18):1815-22.
56. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomized double blind controlled trial. BMJ. 2003 Mar 1;326(7387):469.
57. Lyons RA, Johansen A, Brophy S, et.al. Preventing fractures among older people living in institutional care: a pragmatic randomized double-blind placebo-controlled trial of vitamin D supplementation. Osteoporos Int. 2007 Jun;18(6):811-8.
58. Khaw KT, Stewart AW, Waayer D, et.al Effect of monthly high-dose vitamin D supplementation on falls and non-vertebral fractures: secondary and post-hoc outcomes from the randomized, double-blind, placebo-controlled ViDA trial. Lancet Diabetes Endocrinol. 2017 Jun;5(6):438-447.
59. Lips P, Graafmans WC, Ooms ME, et.al. Vitamin D supplementation and fracture incidence in elderly persons. A randomized, placebo-controlled clinical trial. Ann Intern Med. 1996 Feb 15;124(4):400-6.
60. Meyer HE, Smedshaug GB, Kvaavik E, Falch JA, Tverdal A, Pedersen JI. Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial. J Bone Miner Res. 2002 Apr;17(4):709-15.
61. Grant AM, Avenell A, Campbell MK, et.al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomized Evaluation of Calcium Or vitamin D, RECORD): Lancet. 2005 May 7-13;365(9471):1621-8.
62. Bischoff-Ferrari HA, Vellas B, Rizzoli R, et.al. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. JAMA. 2020 Nov 10;324(18):1855-1868.
63. LeBoff MS, Chou SH, Ratliff KA, Cook NR, Khurana B, Kim E, Cawthon PM, Bauer DC, Black D, Gallagher JC, Lee IM, Buring JE, Manson JE. Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. N Engl J Med. 2022 Jul 28;387(4):299-309
64. Waterhouse M, Sanguineti E, Baxter C, Duarte Romero B, McLeod DSA, English DR, Armstrong BK, Ebeling PR, Hartel G, Kimlin MG, O'Connell RL, Pham H, van der Pols JC, Venn AJ, Webb PM, Whiteman DC, Neale RE. Vitamin D supplementation and risk of falling: outcomes from the randomized, placebo-controlled D-Health Trial. J Cachexia Sarcopenia Muscle. 2021 Dec;12(6):1428-1439
65. LeBoff MS, Murata EM, Cook NR, et.al. Vitamin D and OmegA-3 TriaL (VITAL): Effects of Vitamin D Supplements on Risk of Falls in the US Population. J Clin Endocrinol Metab. 2020 Sep 1;105(9):2929–38.
66. Appel LJ, Michos ED, Mitchell CM, et.al. The Effects of Four Doses of Vitamin D Supplements on Falls in Older Adults: A Response-Adaptive, Randomized Clinical Trial. Ann Intern Med. 2021 Feb;174(2):145-156.
67. Scragg R, Khaw KT, Toop L, et al. Monthly high-dose vitamin D supplementation and cancer risk: a post hoc analysis of the vitamin D assessment randomized clinical trial. JAMA Oncol. 2018;4(11): e182178.
68. Manson JE, Cook NR, Lee IM, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med. 2019; 380(1):33–44.
69. Chatterjee R, Fuss P, Vickery EM, et.al. Vitamin D supplementation for prevention of cancer: the D2d cancer outcomes (D2dCA) ancillary study. J Clin Endocrinol Metab. 2021 Mar 8;106(9):2767–78.

70. Virtanen JK, Nurmi T, Aro A, Bertone-Johnson ER, Hyppönen E, Kröger H, Lamberg-Allardt C, Manson JE, Mursu J, Mäntyselkä P, Suominen S, Uusitupa M, Voutilainen A, Tuomainen TP, Hantunen S. Vitamin D supplementation and prevention of cardiovascular disease and cancer in the Finnish Vitamin D Trial: a randomized controlled trial. Am J Clin Nutr. 2022 May 1;115(5):1300-1310.
71. Keum N, Lee DH, Greenwood DC, et.al. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. Ann Oncol. 2019 May 1;30(5):733-743.
72. Scragg R, Stewart AW, Waayer D, et.al. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study: A Randomized Clinical Trial. JAMA Cardiology. 2017 Jun 1;2(6):608-616.
73. Jorde R, Sollid ST, Svartberg J et.al. Vitamin D 20,000 IU per Week for Five Years Does Not Prevent Progression from Prediabetes to Diabetes. J Clin Endocrinol Metab. 2016 Apr;101(4):1647-55.
74. Pittas AG, Dawson-Hughes B, Sheehan P, D2D Research Group. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med. 2019 Aug 8;381(6):520
75. Centers for Disease Control and Prevention. Asthma: most recent asthma data. Updated March 24, 2020. Accessed August 1,2021. https://www. cdc.gov/asthma/most_recent_data.htm.
76. Forno E, Bacharier LB, Phipatanakul Wet.al Effect of Vitamin D3 Supplementation on Severe Asthma Exacerbations in Children with Asthma and Low Vitamin D Levels: The VDKA Randomized Clinical Trial. JAMA. 2020 Aug 25;324(8):752-760.
77. Castro M, King TS, Kunselman SJ, et.al. Effect of vitamin D3 on asthma treatment failures in adults with symptomatic asthma and lower vitamin D levels: the VIDA randomized clinical trial. JAMA. 2014 May;311(20):2083-91.
78. Jolliffe DA, Greenberg L, Hooper RL, Griffiths CJ, Camargo CA Jr, Kerley CP, Jensen ME, Mauger D, Stelmach I, Urashima M, Martineau AR. Vitamin D supplementation to prevent asthma exacerbations: a systematic review and meta-analysis of individual participant data. Lancet Respir Med.2017Nov;5(11):881-890.
79. Camargo CA Jr, Toop L, Sluyter J, Lawes CMM, Waayer D, Khaw KT, Martineau AR, Scragg R. Effect of Monthly Vitamin D Supplementation on Preventing Exacerbations of Asthma or Chronic Obstructive Pulmonary Disease in Older Adults: Post Hoc Analysis of a Randomized Controlled Trial. Nutrients. 2021 Feb 6;13(2):521.
80. Camargo CA, Sluyter J, Stewart AW, et.al Effect of Monthly High-Dose Vitamin D Supplementation on Acute Respiratory Infections in Older Adults: A Randomized Controlled Trial. Clin Infect Dis. 2020 Jul 11;71(2):311-317.
81. Pham H, Waterhouse M, Baxter C, et.al. The effect of vitamin D supplementation on acute respiratory tract infection in older Australian adults: analysis of data from the D-Health Trial. Lancet Diabetes Endocrinol.2021 Feb;9(2):69-81.
82. Jolliffe DA, Camargo CA Jr, Sluyter JD, et.al. Vitamin D supplementation to prevent acute respiratory infections: a systematic review and meta-analysis of aggregate data from randomized controlled trials. Lancet Diabetes Endocrinol. 2021 May;9(5):276-292.
83. Ganmaa D, Uyanga B, Zhou X et.al. Vitamin D Supplements for Prevention of Tuberculosis Infection and Disease. N Engl J Med. 2020 Jul 23;383(4):359-368.
84. Sudfeld CR, Mugusi F, Muhihi A, Aboud S, Nagu TJ, Ulenga N, Hong B, Wang M, Fawzi WW. Efficacy of vitamin D_3 supplementation for the prevention of pulmonary tuberculosis and mortality in HIV: a randomised, double-blind, placebo-controlled trial. Lancet HIV. 2020 Jul;7(7): e463-e471.
85. Hahn J, Cook NR, Alexander EK, Friedman S, Walter J, Bubes V, Kotler G, Lee IM, Manson JE, Costenbader KH. Vitamin D and marine omega 3 fatty acid supplementation and incident autoimmune disease: VITAL randomized controlled trial. BMJ. 2022 Jan 26;376: e066452.
86. Jolliffe DA, Holt H, Greenig M, Talaei M, Perdek N, Pfeffer P, Vivaldi G, Maltby S, Symons J, Barlow NL, Normandale A, Garcha R, Richter AG, Faustini SE, Orton C, Ford D, Lyons RA, Davies GA, Kee F, Griffiths CJ, Norrie J, Sheikh A, Shaheen SO, Relton C, Martineau AR. Effect of a test-

and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomized controlled trial (CORONAVIT). BMJ. 2022 Sep 7;378: e071230.
87. Brunvoli SH, Nygaard AB, Ellingjord-Dale M, Holland P, Istre MS, Kalleberg KT, Søraas CL, Holven KB, Ulven SM, Hjartåker A, Haider T, Lund-Johansen F, Dahl JA, Meyer HE, Søraas A. Prevention of covid-19 and other acute respiratory infections with cod liver oil supplementation, a low dose vitamin D supplement: quadruple blinded, randomized placebo-controlled trial. BMJ. 2022 Sep 7;378: e071245.
88. Zhao JG, Zeng XT, Wang J, Liu L. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA. 2017 Dec 26;318(24):2466-2482
89. Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med.* 2006; 354:669–683.
90. Robbins JA, Aragaki A, Crandall CJ, Manson JE, Carbone L, Jackson R, Lewis CE, Johnson KC, Sarto G, Stefanick ML, Wactawski-Wende J. Women's Health Initiative clinical trials: interaction of calcium and vitamin D with hormone therapy. Menopause. 2014 Feb;21(2):116-23.
91. Mawer EB, Hann JT, Berry JL, Davies M. Vitamin D metabolism in patients intoxicated with ergocalciferol. Clin Sci (London). 1985 Feb;68(2):135-41.
92. Picolos MK, Lavis VR, Orlander PR. Milk-alkali syndrome is a major cause of hypercalcemia among non-end-stage renal disease (non-ESRD) inpatients. Clin Endocrinol (Oxf). 2005 Nov;63(5):566-76.
93. Machado MC, Bruce-Mensah A, Whitmire M, Rizvi AA. Hypercalcemia Associated with Calcium Supplement Use: Prevalence and Characteristics in Hospitalized Patients. J Clin Med. 2015 Mar 9;4(3):414-24.
94. Gallagher JC, Smith LM, Yalamanchili V. Incidence of hypercalciuria and hypercalcemia during vitamin D and calcium supplementation in older women. Menopause. 2014 Nov:21(11):1173-80
95. Burt LA, Billington EO, Rose MS, et.al. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. JAMA. 2019 Aug 27;322(8):736-745.

Vitamin D Randomized Trials

Outcome	Ref	RR or HR	95%CI	Average Age (yrs)	Number Enrolled	Sex	Trial Length (yrs)	Vitamin D3 Dose (IU)	Serum 25OHD Pre (nmol/L)	Serum 25OHD Post (nmol/L)	Country
Fracture											
Hip Fracture	54	F: 1.82 M: 1.22	F:1.12-2.99 M: 0.52-1.97	79	9,940	F: 51%	3	300,000 annually D2	56	74	UK
Fractures	55	**1.26**	**1.00-1.59**	76	2.256	F:100%	3-5	500,000 annually	49	55-74	Australia
Fractures	56	**0.78** M :0.83 F :0.68	**0.61-0.99** 0.61-1.03 0.46-1.01	84	2686	F: 25%	5	100,000 4 monthly	53	74	UK
Fractures	57	0.95	0.79-1.15	84	3,440	F: 76%	3	100,000 4 monthly	54	80	UK
Fractures	58	0.98	0.92-1.06	66	5,110	F: 41%	3.4	100,000 monthly #	63	117-132	New Zealand
Hip Fracture Peripheral	59	1.18 0.92	0.81-1.71 0.75-1.40	80	2,578	F: 74%	3.5	400 daily	26	62	Netherlands
Hip Fracture Peripheral	60	1.09 0.92	0.73-1.63 0.66-1.27	85	1144	F: 75%	2	400 daily	49	64	Norway
Fractures	61	0.99	0.86-1.15	77	2,675	F:85%	5	800 daily	38	62	UK
Non vertebral Fractures	62	1.03+	0.75-1.43	75	2,157	F: 61%	3	2,000 daily	56	94	Europe
Fractures	63	0.98	0.89-1.08	67	25,871	F: 51%	5.3	2,000 daily	77	103	USA
Falls											
Falls	55	**1.15**	1.00-1.59	76	2.256	F:100%	3-5	500,000 annually	49	55-74	Australia
Falls	57	0.95	0.92-1.45	66	5,110	F: 41%	3.4	100,000 monthly #	63	117-132	New Zealand
Falls	64	1.02	0.95-1.10	60-79	21,315	F: 46%	4.3	60,000 monthly	78	115	Australia
Falls	67	0.97	0.90-1.05	67	25,871	F: 51%	5.3	2,000 daily	77	103	USA
Falls	66	0.94	0.76-1.15	77	647	F: 44%	2	1,000 daily	67 (200 IU)	83 (1,000 IU)	USA

Cancer											
Cancer	56	1.09	0.86-1.36	84	2686	M:75% F: 25%	5	100,000 4 monthly	53	74	UK
Cancer	67	1.01	0.81-1.25	66	5110	F:42%	3.4	100,000 monthly #	63	117-132	New Zealand
Cancer	68	0.96	0.88-1.06	67	25,871	F: 51%	5.3	2,000 daily	77	103	USA
Cancer	69	1.07	0.70-1.62	60	2,423	F: 44%	2-4	4,000 daily	70	135	USA
Cancer	70	1.14 0.95	0.75-1.72 0.61-1.47	68	2495	F:43%	5	1600 IU daily 3200 IU daily	73	100 120	Finland
Cardiovascular											
CVD	56	M 0.91 F 0.89	0.76-1.09 0.63-1.27	84	2686	M:75% F: 25%	5	100,000 4 monthly	53	74	UK
CVD	67	0.97	0.85-1.12	67	25,871	F: 51%	5.3	2,000 daily	77	103	USA
CVD	70	0.97 0.84	0.63-1.49 0.54-1.31	68	2495	F:43%	5	1600 IU daily 3200 IU daily	73	100 120	Finland
CVD	72	1.02	0.87-1.20	66	5110	F:42%	3.4	100,000 monthly #	63	117-132	New Zealand
Type II Diabetes											
Type II Diabetes	73	0.9	0.69-1.18	62	511	F: 39%	5	20,000 weekly	60	122	Norway
Type II Diabetes	74	0.88	0.75-1.04	60	2,423	F: 39 %	2-4	4,000 daily	70	135	USA
Asthma											
Asthma	76	1.13	0.69-1.85	9.8	200	F: 40%	1	4,000 daily	55	123	USA
Asthma	77	0.9	0.60-1.3	40	408	F: 68%	0.6	4,000 daily *	48	105	USA
Upper Respiratory Infection											
URI	80	1.01	0.94-1.07	66	5056	F:41%	3.4	100,000 monthly #	63	135	New Zealand
URI^	81	0.98	0.93-1.02	60-79	25,315	F: 46%	4.3	60,000 monthly	78 (PL)	115 (D)	Australia
Autoimmune diseases	85	0.78	0.61-0.99	67	25,871	F: 51%	5.3	2,000 daily	77	103	USA

* baseline dose 100,000 IU : # baseline dose 200,000 IU + incidence rate ratio. : ^ Odds ratio